REMARKS

Claims 454-575 were previously pending in this application. Claims 454-455, 459, 461, 466, 476, 482-483, 487, 489, 494, 504, 508, 510-531, 533, 535-559, 561 and 563-567 have been amended. Claims 568-575 have been canceled hereinabove. No claims have been added. Accordingly, claims 454-567 as amended are presented for further prosecution on the merits.

A new title of the invention that is believed to be more descriptive of Applicants' claimed invention has been added above. The new title is "Oligo- or Polydeoxyribonucleotides and Oligo- or Polynucleotides Comprising Phosphate Moiety Non-Radioactively Labeled Modified Nucleotides."

In a sincere effort to advance prosecution of this application by reducing or simplifying the issues, Applicants have canceled claims 568-575 above. These claims were the subject of a new matter rejection under 35 U.S.C. §112, first paragraph, which is treated in further detail *infra*.

In a further sincere effort to define their invention more clearly, Applicants have amended several claims above. First, independent claims 454, 482, 511 and 539 have been amended to recite that each such composition is complementary to a nucleic acid of interest or a portion thereof . . . In addition, the polymeric nucleic acid in these independent claims is now defined as comprising at least one modified nucleotide. Further, each of these independent claims has been amended to recite that Sig comprises a non-radioactive label moiety which can be directly or indirectly detected when attached to the phosphate or when the nucleotide is incorporated into the oligo- or polyribonucleotide or when the oligo- or poly(deoxy)nucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof.

In the case of independent claims 511 and 539, the preamble has also been amended to recite "[a]n oligo- or polynucleotide" in place of the former language, "an oligo- or polyribonucleotide." To conform with the aformentioned preamble change in claims 511 and 539, each of the dependent claims (512-531, 535-538, 540-559 and 563-567) has likewise been amended to recite "an oligo- or polynucleotide." In the case of claim 483, the term "polynucleotide" in line 2 has

been changed to "polydeoxyribonucleotide" to conform with the preamble of claim 482 from which it depends. Furthermore, the proviso language in both claims 511 and 539 has been amended to recite that when said oligo- or polynucleotide is an oligoribonucleotide or a polyribonucleotide, and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide. The latter language, particularly the vicinal oxidation recitation, is believed to conform more closely with that in the specification. See the specification, page 53, first full paragraph.[1] The foregoing claim changes, particularly those with respect to the preamble and the language regarding hybridization between the oligo- or poly(deoxy)nucleotide and the complementary nucleic acid of interest follow the discussions held at the August 24, 2000 interview.[2]

Other dependent claims have been amended as follows. Claims 455 and 512 have been amended to recite "wherein said Sig is or renders the nucleotide or the oligo- or polydeoxyribonucleotide" (claim 455) ["or the oligo- or polynucleotide" (in the case of claim 512) "self-signaling or self-indicating or self-detecting." The foregoing changes serve to conform claims 455 and 512 to the language already present in claims 483 and 540, respectively.

A relatively minor symbol change has been made to each of claims 459, 487, 516 and 544. Here, the term "α-position" has been substituted for "alpha-position." A similar symbol change has also been made in the case of claims 461, 489, 518 and 546 where the same term ("α-position") has been substituted, this time, for "delta-position." This latter substitution conforms the claim language with the specification (page 11, second paragraph). Other changes to claims 461, 489,

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[1] The first full paragraph on page 53 in the specification discloses:
Broadly, in another aspect of the practices of this invention various methods are useful for the tagging or labeling of DNA in a non-disruptive manner. For example, biotin is added on the end of a DNA or RNA molecule. The addition of biotin is accomplished by addition of a ribonucleotide. The 3',4' vicinal hydroxyl groups are oxidized by periodate oxidation and then reduced by a borohydride in the presence of biotin hydrazide. Alternatively, carbodiimide can also be used to couple biotin to the aldehyde group.

[2] In the August 24, 2000 Interview Summary, the following description was written:
Applicant's position is the prior art does not attach labels but merely fragments of proteins and that the resulting product can not be used as a probe.

518 and 544 are discussed *infra*.

In yet a further effort to define their invention more clearly and to reduce the issues related to the new matter rejection (35 U.S.C. §112, first paragraph), Applicants have also amended claims 466, 494, 523 and 551. Previously directed to Sig being complexed with a binding protein therefor and such binding protein being conjugated to ferritin, these claims have now been recast in Markush language. Each claim recites "wherein Sig is selected from the group consisting of a ligand and a specific ligand binding protein." The foregoing language is taken from the specification (pages 101-102) which recites:

> The detection of nucleic acids to which specific molecules have been covalently attached can be effected through the use of many naturally occurring proteins to which small molecules are known to specifically bind. In this procedure the small molecules are bound to the nucleotides using the allyl amine side chain. These nucleotides are then incorporated into specific nucleic acids using a DNA or RNA polymerase or ligase chain reaction or a chemical linkage. After annealing this probe with a complementary antiprobe sequence, the presence of the probe is assayed for by the specific binding of the protein to the ligand covalently bound to the probe.
>
> Examples of protein-ligand reactions that are appropriate for this type of detector system include:
> . . .
> 4. Specific ligand binding proteins included in the transport of small molecules. An example of this is the periplasmic binding proteins of bacteria which have been shown to bind many amino acids, glucose, galactose, ribose and other sugars, Pardee, A. Science, 162:632:637 (1968); G. L. Hazelbaur, and J. Adler, Nature New Bio. 230:101-104 (1971)).
>
> In the above-mentioned examples the ligand bound to the nucleic acid reacts with a naturally occurring protein. The specificity of this reaction resides in the ligand-binding site of the protein.

In addition to the minor word change ("α-position" for "delta-position") discussed above, a structural formula for one of the chemical linkages recited in claims 461, 489, 518 and 546 has also been corrected, again to conform the language with the specification (page 11, second and third lines from the bottom of the page). In claims 476, 504, 533, 561, the term "anti-Sig immunoglobulin" has been changed to -- anti-hapten immunoglobulin -- . In addition to rendering the claims more definite, the foregoing amendments are believed to eliminate any

possible new matter issues under 35 U.S.C. §112, first paragraph, by conforming the claim language with the specification, to wit, page 33, last paragraph, through page 34, first paragraph:

> While a single-step "antibody sandwich" method in which one chromosome spread is challenged, post-hybridization, with rabbit anti-biotin IgG may succeed, this protocol may not generate sufficient fluorescence for unambiguous gene assignments. . . Since one also has available monospecific guinea pig anti-DNP IgG, we can haptenize this secondary antibody with biotin and thus generate two ***anti-hapten IgG*** populations, DNP-labeled anti-biotin IgG and biotin-labeled anti-DNP IgG. . . [emphasis added]

Clarifying changes have also been made to five claims (480, 508, 535, 536, 537 and 565). In four of these claims (480, 508, 537 and 565), the word "oxygen" has been substituted for "hydrogen." Thus, claims 480 and 537 now recite "wherein the sugar moiety of said terminal nucleotide has an oxygen atom at each of the 2' and 3' positions thereof." Similarly, claims 508 and 565 now recite "wherein both y and z of said terminal nucleotide comprise an oxygen atom at each of the 3' and 2' positions thereof, respectively." In the case of claim 535, the terms "nucleotide" and "polynucleotide" have been substituted for "ribonucleotide" and "polyribonucleotide," respectively. A similar change has been made to claim 536 where "nucleotide" has been inserted in place of "ribonucleotide." It is believed that the foregoing changes to claims 480, 508, 535, 536, 537 and 565 serve to define more clearly Applicants' claimed invention, particularly with respect to the nature of the labeled terminal nucleotide which can be either a ribonucleotide or a deoxyribonucleotide.

Finally, claims 510 and 567 have been amended both with respect to their chemical structural formula and the definition of the "m" and "n" integers. The structures in claims 510 and 567 now designate the base moiety as "BASE" (and not as "A"). Further, the integers "m" and "n" are now defined as representing "integers from 0 up to about 100,000." The designation of the base moiety as "BASE" merely conforms both dependent claims with the language in claims 482 and 539, from which claims 510 and 567 depend, respectively. Thus, the change is necessary to avoid an issue of improper antecedent basis. The new definition of "m" and "n" is also necessary in order to define both terms in the first instance which are in claims 510 and 567. Thus, a problem of definiteness will be avoided

by allowing this new language which conforms with the specification, pages 23 and 24. See in particular, page 24, lines 4-5 ("wherein m and n represent integers from 0 up to about 100,000").

Entry of the above amendments to the claims is believed to be appropriate and necessary. First, these amendments do not raise new issues which would require further consideration and/or search by the Examiner. In particular, the amendments to the independent claims (454, 482, 511 and 539) with respect to the "probe" aspects of Applicants' claimed nucleic acid compositions follow and incorporate the substance of the August 24, 2000 Interview as set forth in the Interview Summary and discussed in Footnote 2 above. Further, no issue of new matter is raised by the entry of these amendments. Moreover, it is believed that the amendments will actually serve to place this application in better form for appeal by materially reducing or simplifying the issues for appeal. Finally, the amendments do not present additional claims without cancelling a corresponding number of finally rejected claims. In fact, eight claims (569-575) have been canceled above for the purpose of materially reducing or simplifying the issues for appeal. Entry of the amendments is respectfully requested.

Before addressing the substantive issues in the July 18, 2000 Office Action, Applicants would like to acknowledge their appreciation to Examiner Scott Houtteman for the time and courtesy he extended to Drs. Dean L. Engelhardt and Cheryl H. Agris, and to Applicants' undersigned attorney at the interview held on August 24, 2000.

The Rejection Under 35 U.S.C. §112, First Paragraph

Claims 459-472 and 474-575 stand rejected for new matter under 35 U.S.C. §112, first paragraph. In the Office Action (page 2), the Examiner stated:

> Support was not found were indicated in the specification, nor elsewhere, for the following limitations in Claims 459-472 and 474-575:
> Claims 459-463, specific chemical compositions of linkages;
> Claims 464-472, 482-569, specific identity of labels and points of attachment of the "SIG" moiety to internal phosphates;

Claims 474-477 and 570-575, the "composition" limitation, in addition to the above identified limitations.

The new matter is respectfully traversed.

In response, Applicants would like to point out that with respect to claims 568-575, the new matter has been rendered moot in light of the cancellation of these claims. Thus, the remarks below are directed to the new matter rejection insofar as it applies to the remaining pending claims cited in the Office Action.

Ever mindful of the pronouncements on the issue of written description issued in the form of the December 21, 1999 Revised Interim Guidelines (64 FR 71427) and more recently, the January 5, 2001 Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, ¶1, "Written Description" Requirement, Applicants have engaged the services of a patent attorney and former scientist, Dr. Cheryl H. Agris, to address, among others, the new matter rejection. Dr. Agris is submitting a Declaration on behalf of the Applicants.[3] Dr. Agris is a well-respected patent practitioner who has also written and lectured on many patent issues, including written description, enablement and obviousness. Dr. Agris was also a predoctoral fellow who worked in research in the laboratory of Drs. Paul S. Miller and Paul O. P. Ts'o,[4] Department of Biochemistry at the Johns Hopkins University. A copy of Dr. Agris's Declaration is attached to this Amendment as Exhibit A.

After describing her professional work, academic background and research experience in Paragraphs 1-8 (pages 1-4), Dr. Agris points out in Paragraph 9 (pages 4-6) that she has been engaged by the assignee of this application as a scientific and legal consultant to review the prosecution history of U.S. Patent Application Serial No. 08/479,997, filed on June 7, 1995. Dr. Agris also notes that she is being compensated for her review and for making her Declaration. In addition to her review of the prosecution history, Dr. Agris notes that she has also read and reviewed the January 5, 2001 Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, ¶1, "Written Description" Requirement, and

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[3] The complete title of Dr. Agris's Declaration is "Declaration of Dr. Cheryl H. Agris, Attorney At Law (In Support Of The Written Description, Enablement & Non-Obviousness Of The Invention Claimed In U.S. Patent Application Serial No. 08/479,997)."

[4] Drs. Miller and Ts'o's 1981 Biochemistry paper ["Biochemical and Biological Effects of Nonionic Nucleic Acid Methylphosphonates," Biochem. 20(7):1874-1880 (1981)] is the subject of an obviousness rejection under §112, also discussed *infra* and in Dr. Agris's Declaration (Exhibit A).

that her remarks, opinions and conclusions with respect to the written description rejections have been rendered in light of those Guidelines.

After expressing her understanding of the claims to be presented in this application in Paragraph 10 (pages 6-8) of her Declaration (Exhibit A), Dr. Agris reiterates the new matter rejections from the July 18, 2000 and February 3, 1999 Office Actions in Paragraphs 11 and 12 (page 9). In Paragraph 17 (page 12), Dr. Agris defines the level of skill in the art to which the present invention pertains. Based upon her own training, background and experience, Dr. Agris submits that at the time this application was first filed in June 1982, a person of ordinary skill in the art relevant to the subject matter being claimed, including nucleic acid modification, synthesis, hybridization and detection, would have possessed or could have been actively pursuing an advanced degree in organic chemistry and/or biochemistry. Such an ordinarily skilled person could also be at least approaching or ranging toward the level of a junior faculty member with 2-5 years of relevant experience, or at least be a postdoctoral student with several years of experience. Dr. Agris considers herself to possess the level of skill and knowledge of at least a person of ordinary skill in the art to which the present application and invention pertains.

Later, in Paragraphs 18-30 (pages 12-28), Dr. Agris addresses each of the three issues set forth in the written description rejection. For the sake of accuracy and completeness, Dr. Agris's statements are set forth below.

As characterized by Dr. Agris in Paragraph 18 (page 12) of her Declaration (Exhibit A), the written description rejection concerns three issues:

A. the specific chemical compositions of linkages recited in claims 459-463;

B. the specific identity of labels and points of attachment of the "SIG" moiety to internal phosphates as recited in claims 464-472 and 482-569; and

C. the composition limitations as recited in claims 474-477 and 570-575.

A. **Specific chemical compositions of linkages (claims 459-463)**

In Paragraph 19 (page 13), Dr. Agris indicates her understanding that claims 459-463 are directed to subject matter where

the chemical linkage comprises a member selected from the group consisting of an olefinic bond at the α-position relative to the point of attachment to the nucleotide, a $-CH_2NH-$ moiety, or both (claim 459);

the chemical linkage comprises an allylamine group (claim 460);

the chemical linkage comprises or includes an olefinic bond at the α-position relative to the point of attachment to the nucleotide, or any of the moieties:

$$-CH=CH_2-NH-$$

$$-CH=CH-CH_2-NH-$$

$$-CH=CH-CH_2-O-CH_2-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-NH-,$$

$$-S-,\quad -\overset{\displaystyle O}{\overset{||}{C}}-O,\text{ and } -O- \text{ (claim 461);}$$

the chemical linkage of Sig includes a glycosidic linkage moiety (claim 462); and PM is a monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached to said PM through a phosphorus atom or phosphate oxygen (claim 463).

In Paragraph 20 (pages 13-14), Dr. Agris avers that as a person skilled in the art to which the present invention pertains, she have reviewed the '997 specification as originally filed and that it is her opinion and conclusion that the following portions of that disclosure support the above recited chemical linkages:

Chemical Linkage(s)	Citation In Specification	Description in Disclosure
olefinic bond at the α-position relative to the point of attachment to	Page 11, 2nd ¶ Original Claim 78	that the chemical linkage include an olefinic bond at the α-position relative to B
the nucleotide, a $-CH_2NH-$ moiety, or both	Page 11, last ¶ Original Claim 79	that the chemical linkage group . . . have the structure $-CH_2NH-$, . . .
an allylamine group	Page 11, last ¶ Original Claim 80	Examples of preferred linkages derived from allylamine . . .

Chemical Linkage(s)	Citation In Specification	Description in Disclosure
olefinic bond at the α-position relative to the point of attachment to the nucleotide or any of the moieties	Page 11, 2nd ¶	preferred that the chemical linkage include an olefinic bond at the α-position relative to B. The presence of such an α-olefinic bond . . .
$-CH=CH_2-NH-$ $-CH=CH-CH_2-NH-$ $-CH=CH-CH_2-O-CH_2-CH(OH)-CH_2-NH-$	Page 11, line 29 Page 11, l. 29-30	$-CH=CH-CH_2-NH-$ $-CH=CH-CH_2-O-CH_2-CH(OH)-CH_2-NH-$
$-S-$	Original Claim 82	$-S-$
$-C(=O)-O-$	*ibid.*	$-C(=O)-O-$
$-O-$	*ibid.*	$-O-$
glycosidic linkage moiety	Original Claim 25	said Sig chemical moiety is attached by or includes a glycosidic linkage moiety.
PM is a monoP, diP triP and said Sig moiety is covalently attached to said PM through a phosphorus atom or phosphate oxygen	Page 9, lines 8-14	wherein each of x, y and z represents H–, HO–, $HO-P(=O)(OH)-O-$ . . .
	Page 57, Ex. V	Biotin and polybiotinylated poly-L-lysine were coupled to oligoribonucleotides using a carbodiimide coupling procedure described by Halloran and Parker, J. Immunol., 96 373 (1966).

Dr. Agris concludes Paragraph 20 by indicating that it is her opinion and conclusion as a person skilled in the art that the above-cited portions in the disclosure fully support the various chemical linkages recited in the pending claims of this application. According to Dr. Agris, the above-cited portions describe such recited chemical linkages in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of such chemical linkages.

B. **Specific identity of labels and points of attachment of th "SIG" moiety to internal phosphates (claims 464-472 and 482-569)**

In Paragraph 21 (pages 15-16), Dr. Agris expresses her understanding that claims 464-472 and 482-567 (claims 568-569 having been canceled) are directed to subject matter for the following labels of the "SIG" moiety:

Labels (SIG)

Claims 464, 492, 521 and 549 (Listed as (i) through (xvi) below)

(i) biotin

(ii) iminobiotin

(iii) electron dense component

ferritin (claims 465, 493, 522 and 550)

(iv) ligand and a specific ligand binding protein (claims 466, 494, 523 and 551 as amended)

(v) magnetic component

magnetic oxide (claims 467, 495, 524 and 553)

ferric oxide (claims 468, 498, 525 and 552)

(vi) enzyme or an enzyme component

alkaline phosphatase, acid phosphatase, β-galactosidase, ribonuclease, glucose oxidase and peroxidase (claims 469, 497, 526 and 554);

(vii) hormone or a hormone component

(viii) metal-containing component

catalytic (claims 470, 498, 527 and 555)

(ix) fluorescent component

fluorescein, rhodamine and dansyl (claims 471, 499, 528 and 556)

(x) chemiluminescent component

(xi) antigen

(xii) hapten

(xiii) antibody or an antibody component

antigen or hapten capable of complexing with an antibody or antibody component specific thereto, and an antibody or antibody component capable of complexing with an antigen or hapten (claims 472, 500, 529 and 557);

(xiv) composition comprising the oligo- or polydeoxyribonucleotide . . ., a polypeptide capable of forming a complex with Sig and a moiety which can be detected when such complex is formed (claims 502, 531 and 559); polypeptide comprises polylysine (claims 503, 532 and 560); polypeptide is selected from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin (claims 504, 533 and 561);

(xv) composition of . . ., wherein Sig is a ligand and said polypeptide is an antibody thereto (claims 505, 534 and 562); and

(xvi) Sig is or renders the nucleotide or the oligo- or polynucleotide self-signaling or self-indicating or self-detecting (claims 512 and 540).

In Paragraph 22 (pages 16-19), Dr. Agris avers that she has reviewed the '997 specification as originally filed and that it is her opinion and conclusion as a skilled person in the art that the following portions of that disclosure support the above recited labels or SIG listed as items (i) through (xvi):[5]

Label (Sig)	Citation In Specification	Description in Disclosure
biotin	Page 10, last 2 lines	. . . the preferred A moieties are biotin and iminobiotin.
	Page 97, last ¶, thru Page 98, 1st 4 lines	. . . the chemical moiety A . . . is functionally the equivalent of the Sig component or chemical moiety . . . of this invention.
	Original Claim 92	. . Sig chemical moiety is biotin
iminobiotin	*ibid.*	
electron dense component	Page 97, 1st ¶	The Sig moiety might also include an electron dense component, . . .
ferritin	*ibid.*	such as ferritin, . . .

[5] As noted in footnote 2 (page 16) of Dr. Agris's Declaration, "The citations and descriptions listed below are not necessarily intended to be exhaustive of all the support for any given label or Sig. Rather, the citations and descriptions are offered as illustrative support which is non-limiting.

Label (Sig)	Citation In Specification	Description in Disclosure
ligand and a specific binding protein	Page 101, thru Page 102	. . presence of probe is assayed for by the specific binding of the protein to the ligand . . .
magnetic component	Page 97, 1st ¶	magnetic component associated or attached thereto, . . .
magnetic oxide	*ibid.*	such as a magnetic oxide,
ferric oxide	*ibid.*	or magnetic iron oxide, . . .
enzyme or an enzyme component:	Page 96, 2nd ¶	The Sig moiety could comprise an enzyme or enzymic material
alkaline phosphatase	*ibid.*	such alkaline phosphatase,
acid phosphatase	Original Claim 41	said enzyme is acid phosphatase
	Original Claim 197	group . . . acid phosphatase . . .
β-galactosidase	Page 36, 3rd ¶ Also Original Claim 84	direct enzymes such as . . . or β-galactosidase . . . said enzyme is β-galactosidase.
ribonuclease	Page 96, 2nd ¶	or ribonuclease.
glucose oxidase	*ibid.*	glucose oxidase,
peroxidase	*ibid.*	horseradish peroxidase,
hormone or a hormone component	Page 102, 1st ¶	3. Hormone receptors and other receptors on the surface of the cell . . .
metal-containing component	Original Claim 28	. . metal-containing component
catalytic	Original Claim 83	said Sig chemical moiety includes or comprises a catalytic metal component
	Original Claim 174	. . . catalytically active metal.
fluorescent component	Page 96, 1st ¶	The Sig moiety could include a fluorescing component
fluorescein, rhodamine or dansyl	*ibid.*	such as fluorescein or rhodamine or dansyl.

Label (Sig)	Citation In Specification	Description in Disclosure
chemiluminescent component	Page 97, 1st ¶	The Sig component or moiety could include . . . a chemiluminescent component
antigen	Original Claim 28 See also Page 88, 2nd ¶	an antigen . . . fix to a solid matrix a specific antigen and bind to this antigen an antibody directed against this antigen which itself has been biotinylated.
hapten	Page 97, 1st ¶	could include a hapten component
antibody or an antibody component	Original Claim 28	or antibody component.
antigen or hapten capable of complexing with antibody . . .	Original Claim 136	said Sig chemical moiety includes an antigenic or hapten component capable of complexing with an antibody specific to said component.
antibody or an antibody component capable of complexing with an antigen or hapten	*ibid.* See also Page 88, last ¶	The use of the antigen-antibody system for detecting either antigen or antibody is well known.
composition . . . oligo- or polynucleotide . . polypeptide and moiety which can be detected	Original Claims 167 & 168	A polynucleotide comprising one or more nucleotides . . . coupled to a polypeptide, . . . having attached . . . one or more Sig chemical moieties
polypeptide . . . polylysine	Original Claim 56	said polypeptide is a polylysine.
polypeptide . . . avidin, streptavidin and anti-hapten immunoglobulin	Page 25, last 2 lines Page 26, 3rd ¶ Page 34, 1st ¶	One polypeptide detector for the biotinyl-type probe is avidin. A preferred probe for biotin-containing nucleotides and derivatives is streptavidin, an avidin-like protein . . . We can haptenize this secondary antibody with biotin and thus generate two anti-hapten IgG populations, . . .

Label (Sig)	Citation In Specification	Description in Disclosure
Sig is a ligand and said polypeptide is an antibody	Page 101, 1st ¶	. . presence of probe is assayed for by the specific binding of the protein to the ligand . . .
self-signaling or self-indicating or self-detecting	Page 82, 1st ¶	Of special importance and significance . . . self-signaling or self-indicating or self-detecting nucleic acids,

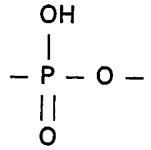
Dr. Agris completes Paragraph 22, indicating that it is her opinion and conclusion as a person skilled in this art that the above-cited portions in the disclosure fully support the various labels which embody Sig in the pending claims of this application. Dr. Agris further indicates that the above-cited portions are in general quite explicit and describe the claimed labels or Sig in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of such claimed labels or Sig.

Attachment of SIG to Internal Phosphates

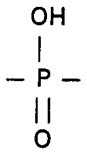
In Paragraph 23 (pages 19-21), Dr. Agris expresses her understanding of the following claims with respect to being directed to the points of attachment of the "SIG" moiety to internal phosphates:

An oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the structural formula . . . wherein x, y and z are selected from the group consisting of H— , HO— , a mono-phosphate, a di-phosphate and a tri-phosphate and wherein Sig is covalently attached directly or through a chemical linkage to at least one phosphate selected from the group consisting of x, y, z, and a combination thereof . . . (claim 482);

oligo- or polydeoxyribonucleotide of . . . wherein said covalent attachment is selected from . . .



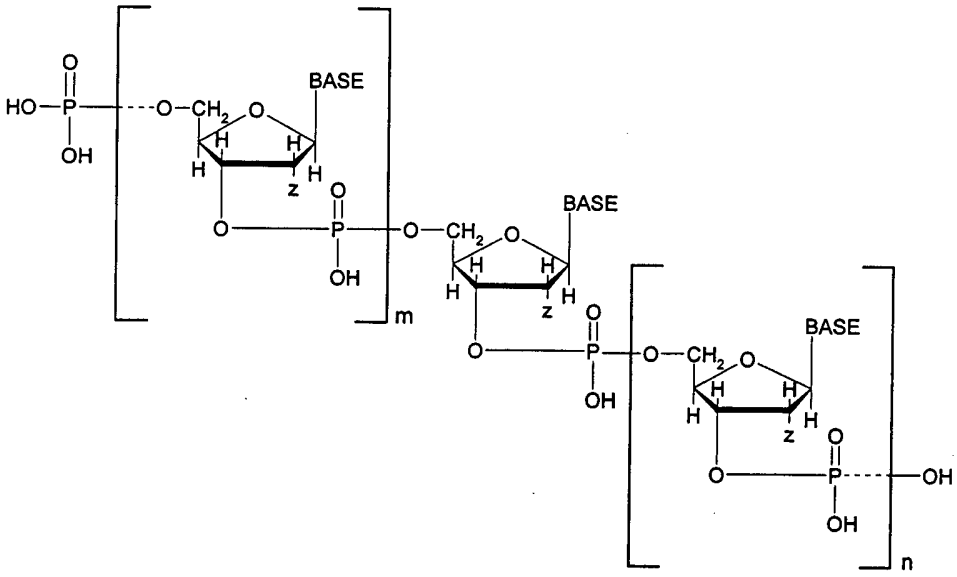
and



(claims 485, 514 and 542)

oligo- or polydeoxyribonucleotide of . . . wherein said x and y each comprise a member selected from the group consisting of mono-, di or tri-phosphate and said Sig moiety is covalently attached to either or both of said x and y through a phosphorus or phosphate oxygen(claim 491, 520 and 548);

oligo- or polydexoyribonucleotide of . . . having the structural formula:

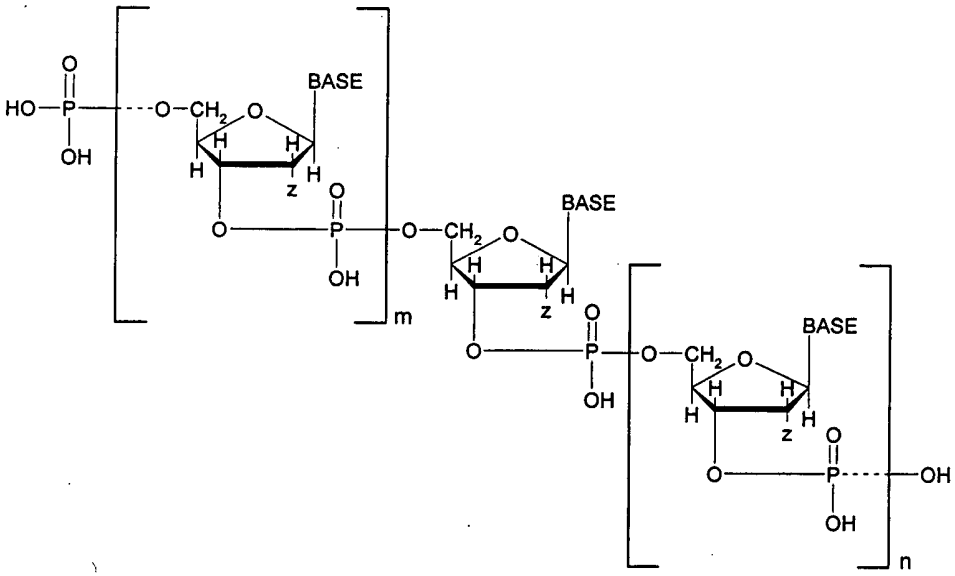


wherein said Sig moiety is attached to at least one of the phosphate moieties in said structural formula (claim 510);

oligo- or polynucleotide . . . having the structural formula Sig – PM – SM – BASE . . . Sig is covalently attached to PM directly or via a chemical linkage (claim 511) [recited in Paragraph 10C above];

oligo- or polyribonucleotide comprising at least one nucleotide having the structural formula . . . Sig is covalently attached to x, y or z directly or through a chemical linkage (claim 539) [recited in Paragraph 10D above]; and

oligo- or polyribonucleotide of . . ., having the structural formula:



wherein said Sig moiety is attached to at least one of the phosphate moieties in said structural formula (claim 567).

In Paragraph 24 (page 21), Dr. Agris states that she has reviewed the '997 specification as originally filed and that as a person of ordinary skill in the art, it is her opinion and conclusion that the original disclosure sufficiently describes the attachment of the Sig moiety to the phosphorus atom as to reasonably convey that Applicants had possession of such claimed subject matter at the time the invention was made in June 1982.

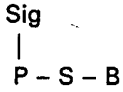
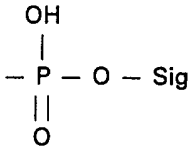
In Paragraph 25 (pages 21-22), Dr. Agris notes as a patent practitioner, she has lectured and written on the requirements of 35 U.S.C. §112, including the Written Description requirements under the first paragraph of §112. Dr. Agris further notes that she has also submitted comments on the Interim Written Description Guidelines issued July 7, 1998, 63 FR 32,639. Dr. Agris points out that Applicants' disclosure and their claimed subject matter also meets the January 5, 2001 Written Description Guidelines (Exhibit 7 of her Declaration), particularly with respect to the attachment of Sig to the phosphorus atom of the phosphate moiety. As set forth by Dr. Agris, those guidelines provide that the written description requirement is met when the patent specification describes the claimed invention in "sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention" (citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991) 66 FR 1099 (2001).

According to these guidelines, possession may be shown by showing that the invention was "ready for patenting" such as by the disclosure of drawings or other descriptions of the invention that are sufficiently specific to enable a person skilled in the art to practice the invention. *Id.* It is well established case law that when the elements recited in the claims are supported by corresponding language in the text, examples, drawings, or other disclosure in the specification, the written description requirement is satisfied and no further analysis is required. *In re Bowen*, 492 F.2d 859 (C.C.P.A. 1974). Furthermore, if new claims are proposed during prosecution, each claim must be expressly, implicitly or inherently supported in the originally filed disclosure and each claim must include all elements which applicant has described as essential. 66 FR at 1105. To establish inherency, it must be clear from any extrinsic evidence provided in the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill. *In re Robertson*, 169 F.3d 743, 49 USPQ2d 1949 (Fed. Cir. 1999).

Dr. Agris points out in Paragraph 26 (page 22) that training materials have also been provided in connection with the Revised Interim Written Description Guidelines issued on December 21, 1999, and that a decision tree was included with those training materials and is attached to her Declaration as Exhibit 8. According to Dr. Agris, although revisions are expected to the training materials in view of the final Written Description Guidelines, these training materials appear to be still in effect. 66 FR at 1099. When a claim of broader scope is added, the question posed is "Is an element(s) missing from the claim?" If the answer is "yes", the question posed is "Is the missing element(s) described by applicant as being an essential or critical feature of the new claim as a whole?" If the answer is "no", the question posed is "Is there express, inherent or implicit support for the claim as a whole?" If the answer is "yes", the written description requirement is met.

For reasons explained in four subsections (A-D) of Paragraph 27 (pages 22-26), Dr. Agris states that it is her opinion and conclusion that the written description requirement has been met. The four subsections (A-D) of Paragraph 27 are set forth below.

A. First, several structures are depicted and descriptions given where "Sig" is attached to the phosphate moiety. As described on pages 8-10 in the Engelhardt Declaration (Exhibit 6), such structures are found variously in the specification, for example, on page 94, last paragraph, and continuing through page 95, first paragraph:

> Still further, nucleotides in accordance with the practices of this invention include the nucleotides having the formula
>
> 
>
> wherein P is the phosphoric acid moiety, S the sugar moiety and B the base moiety. In these special nucleotides the P moiety is attached to the 3' and/or the 5' position of the S moiety when the nucleotide is deoxyribonucleotide and at the 2', 3' and/or 5' position when the nucleotide is a ribonucleotide. The base B is either a purine or a pyrimidine and the B moiety is attached from the N1 or the N9 position to the 1' position of the sugar moiety when said B moiety is a pyrimidine or a purine, respectively. The Sig chemical moiety is covalently attached to the phosphoric acid P moiety via the chemical linkage
>
> 
>
> said Sig, when attached to said P moiety being capable of signalling itself or making itself self-detecting or its presence known and desirably the nucleotide is capable of being incorporated into a double-stranded or DNA, RNA or DNA-RNA hybrid.

Later in the specification, on page 96, and continuing through the first paragraph on page 98, other descriptions are provided wherein Sig is attached to the phosphate moiety:

> By way of summary, as indicated hereinabove with respect to the make-up of the various special nucleotides in accordance with this invention, the special nucleotides can be described as comprising a phosphoric acid moiety P, a sugar moiety S and a base moiety B, a purine or pyrimidine, which combination of P-S-B is well known with respect to and defines nucleotides, both deoxyribonucleotides and ribonucleotides. The nucleotides are then modified in accordance with the practices of this invention by having covalently attached thereto, to the P moiety and/or the S moiety and/or the B moiety, a chemical moiety Sig. The chemical moiety Sig so attached to the nucleotide P-S-B is capable of rendering or making the resulting nucleotide, now comprising P-S-B with the Sig moiety attached to one or more of the other moieties, self-detecting or signalling itself or capable of making its presence known per se, when incorporated into a polynucleotide, especially a double-stranded polynucleotide, such as double-stranded

DNA, a double-stranded RNA or a double-stranded DNA-RNA hybrid. The Sig moiety desirably should not interfere with the capability of the nucleotide to form a double-stranded polynucleotide containing the special Sig-containing nucleotide in accordance with this invention and, when so incorporated therein, the Sig-containing nucleotide is capable of detection, localization or observation.

The Sig moiety employed in the make-up of the special nucleotides of this invention could comprise an enzyme or enzymic material, such as alkaline phosphatase, glucose oxidase, horseradish peroxidase or ribonuclease. The Sig moiety could also contain a fluorescing component, such as fluorescin or rhodamine or dansyl. If desired, the Sig moiety could include a magnetic component associated or attached thereto, such as a magnetic oxide or magnetic iron oxide, which would make the nucleotide or polynucleotide containing such a magnetic-containing Sig moiety detectable by magnetic means. The Sig moiety might also include an electron dense component, such as ferritin, so as to be available by observation. The Sig moiety could also include a radioactive isotope component, such as radioactive cobalt, making the resulting nucleotide observable by radiation detecting means. The Sig moiety could also include a hapten component or per se be capable of complexing with an antibody specific thereto. Most usefully, the Sig moiety is a polysaccharide or oligosaccharide or monosaccharide, which is capable of complexing with or being attached to a sugar or polysaccharide binding protein, such as a lectin, e.g. Concanavilin A. The Sig component or moiety of the special nucleotides in accordance with this invention could also include a chemiluminescent component.

As indicated in accordance with the practices of this invention, the Sig component could comprise any chemical moiety which is attachable either directly or through a chemical linkage or linker arm to the nucleotide, such as the base B component therein, or the sugar S component therein, or the phosphoric acid P component thereof.

The Sig component of the nucleotides in accordance with this invention and the nucleotides and polynucleotides incorporating the nucleotides of this invention containing the Sig component are equivalent to and useful for the same purposes as the nucleotides described in the above-identified U.S. patent application Serial No. 255,223. More specifically, the chemical moiety A described in U.S. patent application Serial No. 255,223 is functionally the equivalent of the Sig component or chemical moiety of the special nucleotides of this invention. Accordingly, the Sig component or chemical moiety of nucleotides of this invention can be directly covalently attached to the P, S or B moieties or attached thereto via a chemical linkage or linkage arm as described in U.S. patent application Ser. No. 255,223, as indicated by the dotted line connecting B and A of the nucleotides of U.S. Serial No. 255,223. The various linker arms or linkages indentified in U.S. Ser. No. 255,223 are applicable to and useful in the preparation of the special nucleotides of this invention.

B. Furthermore, as set forth on pages 10-11 of the Engelhardt

Declaration (Exhibit 6), there are nine separate instances where Sig is described in the specification as being attached to the phosphate moiety P (as well as the sugar moiety S and/or the base moiety B):

Specification	Description
page 90, last paragraph	. . . and a signalling chemical moiety Sig covalently attached thereto, either to the P, S or B moiety.
page 93, first paragraph	. . . include a chemical moiety Sig covalently attached to the P, S and/or B moieties.
page 96, first paragraph	. . . by having covalently attached thereto, to the P moiety and/or the S moiety and/or the B moiety, a chemical moiety Sig.
page 98, first paragraph	. . . the Sig component or chemical moiety of nucleotides of this invention can be directly covalently attached to the P, S or B moieties or attached thereto via a chemical linkage or linkage arm . . .
page 103, first full paragraph	. . . and the signalling or self-detecting moiety, Sig, covalently attached to either the P, S or B moieties, as indicated hereinabove, . . .
page 104, first paragraph	. . . nucleotides in accordance with this invention containing the above-described components P, S, B and Sig . . .
page 105, first paragraph	. . . the nucleotides of this invention include the P, S, B and Sig components wherein the Sig is covalently attached to either the P, S or B moieties
page 105, second paragraph	The moiety Sig attached to the special nucleotides of this invention containing the other moieties or components P, S, B provide a site per se for the attachment thereto, the Sig component, . . .
page 106, first paragraph	. . . the special P, S, B and Sig-containing nucleotides of this invention, . . .

Upon seeing such structures and their descriptions in the specification, one of ordinary skill in the art would clearly understand that "Sig" may be attached to either the oxygen or phosphorus atom of the phosphate moiety. As described in the Engelhardt Declaration (Exhibit 6), methods are provided in the specification and are well known in the art for attaching a substituent to the phosphorus and to the oxygen atom. Therefore, in [Dr. Agris's] opinion, the written description

requirement has been met.

C. Thirdly, [Dr. Agris holds] the same opinion and [she has] reached the same conclusion in applying the analysis set forth in the decision tree in the training materials (Exhibit 8) provided in connection with the Written Description Guidelines. As a person of ordinary skill in the art, [Dr. Agris] also [recognizes] that the scope of claims 459-472 and 474-567 is somewhat broader than the original claims. Specifically, the originally filed claims (see, for example, original claims 141) contained the requirement that "Sig" be attached to the oxygen atom in the phosphate moiety (PM). The currently pending claims do not contain such a requirement. This missing element is not an essential or critical feature of the new claims as a whole because there is no specific requirement set forth in the specification that "Sig" be attached to the oxygen atom in the phosphate moiety.

D. Further, in [Dr. Agris's] opinion and conclusion, there is inherent support for the subject matter of claims 459-474 and 474-567. As a person of ordinary skill in the art, it is [Dr. Agris's] opinion and conclusion that a reading of the specification, including Example V and the extrinsic evidence detailed in the Engelhardt Declaration (Exhibit 6), reasonably conveys that in accordance with the present invention, when a substituent is depicted as being attached to a phosphate moiety (PM), that such a substituent could be attached to either an oxygen or phosphorus atom.

At the end of Paragraph 27 (page 26), Dr. Agris states that it is her opinion and conclusion that Applicants' claimed subject matter wherein the Sig moiety is attached to the phosphorus or oxygen atom of the phosphate moiety meets the requirements for written description.

C. **Composition limitations (claims 474-477 and 570-575)**

In Paragraph 28 (pages 26-27), Dr. Agris directs her remarks to claims 474-477 which contain the following subject matter:

a composition comprising the oligo- or polydeoxyribonucleotide of claim 454, a polypeptide capable of forming a complex with Sig and a moiety which can be

detected when such complex is formed (claim 474);

the composition . . . wherein said polypeptide comprises polylysine (claim 475);

the composition . . . wherein said polypeptide is selected from the group consisting of avidin, streptavidin and anti-Sig immunoglobulin (claim 476); and

the composition . . . wherein Sig is a ligand and said polypeptide is an antibody thereto (claim 477).

In Paragraph 29 (page 27), Dr. Agris states that she has reviewed the '997 specification as originally filed and that it is her opinion and conclusion as a skilled person in the art that the following portions of that disclosure support the above recited compositions:

Composition(s)	Citation In Specification	Description in Disclosure
comprising oligo- or polydeoxyribonucleotide . . . , a polypeptide capable of forming a complex with Sig and a moiety which can be detected when such complex is formed	Page 8, last ¶ Page 97, last ¶, thru Page 98, 1st 4 lines	wherein A represents a moiety . . . which is capable of forming a detectable complex with a polypeptide . . . the chemical moiety A described in U.S. patent application Serial No. 255. 223 is functionally the equivalent of the Sig component or chemical moiety . . . of this invention.
wherein said polypeptide comprises polylysine	Original Claim 56	said polypeptide is a polylysine.
polypeptide . . . avidin, streptavidin and anti-hapten immunoglobulin	Page 25, last 2 lines Page 26, 3rd ¶ Page 34, 1st ¶	One polypeptide detector for the biotinyl-type probe is avidin. A preferred probe for biotin-containing nucleotides and derivatives is streptavidin, an avidin-like protein . . . We can haptenize this secondary antibody with biotin and thus generate two anti-hapten IgG populations, . . .
Sig is a ligand and said polypeptide is an antibody	Page 101, 1st ¶	. . presence of probe is assayed for by the specific binding of the protein to the ligand . . .

In Paragraph 30 (page 27, through the first line on page 28), Dr. Agris states

that based upon the above-cited portions, it is her opinion and conclusion as a person skilled in the art that the specification as originally filed fully supports the compositional subject matter in claims 474-477. Dr. Agris further states that she finds that the disclosure provides sufficient detail that a person skilled in the art can reasonably conclude that the inventors had possession of the subject matter in claims 474-477 at the time the application was originally filed in June 1982.

In view of the submission of Dr. Agris's Declaration (Exhibit A), Applicants respectfully request reconsideration and withdrawal of the new matter rejection.

The Rejection Under 35 U.S.C. §112, First Paragraph

Claims 454-575 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record. In the Office Action (pages 3-4), the Examiner stated:

> Halloran et al., J. Immunol. 96(3):373-378, 1966 (Halloran) discloses the attachment of a specific signal moiety, a protein, to the phosphorus atom of the phosphate moiety using a specific linker, a -C-(CHZ)4-N- chain. In contrast, the claims are drawn to a much broader category, a generic "SIG" moiety and linkage, and specific compounds such as those recited in claim 464-magnetic, hormone, metal containing "SIG" moieties, for example.) Thus, the scope of the enablement is not commensurate with the scope of the claims.
>
> In addition, several of the reference articles are drawn to labeling a mononucleotide and express doubt about labeling an oligonucleotide. Armstrong et al., Eur. J. Biochem. 0:33-38, 1976, teaches that the labeled mononucleotides are "strong competitive inhibitors" of the reaction which is necessary to produce a labeled oligonucleotide from a labeled mononucleotide. See Armstrong, p. 33, col. 1. This reaction is the use of the labeled mononucleotide as a substrate for the polymerase mediated synthesis of the oligonucleotide.
>
> While Armstrong teaches that some labeled mononucleotide will be incorporated, Armstrong teaches no guidance as to which of the myriad labels within the scope of these claims will function in the claimed invention. Lacking any guidance in the specification and in view of the breadth of the claims, it would require undue experimentation in order to enable a reasonable number of embodiments of these claims. The skilled artisan would have to

> experiment with various SIG moieties, linkages and attachment sites, as well as various reaction protocols and protecting groups.
>
> The enablement rejection is respectfully traversed.

In response, Applicants offer the Declaration of Dr. Cheryl H. Agris (Exhibit A) and her statements on the enablement issue.

In Paragraph 31 (page 28) of her Declaration (Exhibit A), Dr. Agris states that as a person of at least ordinary skill in the art to which the present invention pertains, it is her opinion and conclusion that the original disclosure of the '997 specification was enabling and permitted the practice of the subject matter of claims 454-567 without undue experimentation. Her reasons for concluding that the '997 specification is enabling are set forth on pages 28 and 29 of her Declaration.

According to Dr. Agris in Paragraph 32 (page 28), although Halloran et al. only teaches one moiety, other moieties are disclosed in the specification and are known in the art. Specifically, Example V of the instant specification discloses a method for attaching biotin, one of the embodiments for Sig, to the phosphate moiety of a mononucleotide and an oligonucleotide that are coupled to a protein, poly-L-lysine. Furthermore, as detailed on pages 11 and 12 in the Engelhardt Declaration (Exhibit 6), the chemistry and reactions for attaching substituents to the oxygen or phosphorus atoms in a nucleotidyl phosphate or phosphoric acid moiety were already known in the art at the time the initial application was filed in June 1982.

In Paragraph 33 (pages 28-29), Dr. Agris responds to statements made in the July 18, 2000 Office Action regarding the Armstrong et al. reference where it is stated on page 3 in that Office Action that:

> Armstrong et al., Eur. J. Biochem. 70:33-38, 1976, teaches that the labeled mononucleotides are "strong competitive inhibitors" of the reaction which is necessary to produce a labeled oligonucleotide from a labeled mononucleotide. See Armstrong, p. 33, col. 1. This reaction is the use of the labeled mononucleotide as a substrate for the polymerase mediated synthesis of the oligonucleotide.

The conclusion is reached in the Office Action that:

> . . . Lacking any guidance in the specification and in view of the breadth of the claims, it would require undue experimentation in order to enable a reasonable number of embodiments of these claims. The skilled artisan would have to experiment with various SIG moieties, linkages and attachment sites, as well as various reaction protocols and protecting groups.

Dr. Agris responds to the above in her Declaration, indicating that it is her opinion and conclusion as a person skilled in the art that the labeled mononucleotides referenced in Armstrong et al. were strong competitive inhibitors because unmodified nucleoside triphosphates (NTPs) were present in the assay mixture. This would not be the case or a factor in the present invention according to Dr. Agris. Armstrong et al. actually show that it is possible to incorporate such modified mononucleotides and that modified NTPs may be used as substrates. Although Armstrong et al. does disclose that some modified nucleotides are better than others in terms of binding to RNA polymerase, a person skilled in the art would expect that some routine testing or refinement is necessary.

In light of Dr. Agris's Declaration and her statements on enablement offered as a person skilled in the art, Applicants respectfully request that the enablement rejection be reconsidered and withdrawn.

The First Rejection Under 35 U.S.C. §103

Claims 454-575 stand rejected under 35 U.S.C. §103 for being unpatentable over Gohlke et al., U.S. Patent No. 4,378,458, filed 3/1981 in view of Sodja et al., Nucleic Acids Research 5(2):385-401 (1978) and further in view of applicant's admissions for reasons of record.

In response to the first obviousness rejection, Applicants offer the Declaration of Ann Sodja, Ph.D.,[6] the co-author of the above cited Sodja et al. 1978 article, and presently a tenured Associate Professor in the Department of Biological Sciences at Wayne State University in Detroit, Michigan.

[6] **The complete title of Dr. Sodja's Declaration is "Declaration of Dr. Ann Sodja (In Support Of The Non-Obviousness Of The Invention Claimed In U.S. Patent Application Serial No. 08/479,997)."**

After describing her professional work, academic background, research experience and scientific publications in Paragraphs 1-4 (pages 1-3), Dr. Sodja points out in Paragraph 5 (page 3) that she has been engaged as a scientific consultant by the assignee in order to review the prosecution of this application. Dr. Sodja also states that she is being compensated for the review and the Declaration she is making in this application.

In Paragraph 6 (pages 4-5), Dr. Sodja describes her understanding of the obviousness rejection at hand. In Paragraph 7 (pages 5-8), Dr. Sodja sets forth her understanding of the claimed invention as represented by the independent embodiments (claims 454, 482, 511 and 539). Dr. Sodja defines in Paragraph 9 (page 8) the level of skill in the art. According to Dr. Sodja, based upon her own training, background and experience, she submits that at the time this application was first filed in June 1982, a person of ordinary skill in the art relevant to the subject matter being claimed, including nucleic acid modification, synthesis, hybridization and detection, would have possessed or could have been actively pursuing an advanced degree in organic chemistry and/or biochemistry. Such an ordinarily skilled person could also be at least approaching or ranging toward the level of a junior faculty member with 2-5 years of relevant experience, or would at least be a postdoctoral student with several years of experience. Dr. Sodja considers herself to possess the level of skill and knowledge of at least a person of ordinary skill in the art to which the present application and invention pertains.

In Paragraph 10 (page 8), Dr. Sodja states that it is her opinion and conclusion that the subject matter of claims 454-567 would not have been rendered obvious at the time the invention was made from a combined reading of the Gohlke's '458 Patent in view of her own publication, Sodja et al., and further in view of applicant's admissions for reasons of record. Dr. Sodja's provides her reasons in Paragraphs 11-16 (pages 8-11) of her Declaration.

As the author of the cited Sodja and Davidson (1978) (Exhibit 2 in her Declaration), Dr. Sodja points out in Paragraph 11 (pages 8-9) that her work was intended to help Dr. Davidson and her with electron microscopic gene mapping and gene enrichment of DNA:RNA hybrids. By coupling cytochrome-c to the oxidized 2', 3' terminus of RNA and attaching biotin labels to the coupled cytochrome-c,

Drs. Sodja and Davidson found that electron microscopic gene mapping could be carried out efficiently with avidin-ferritin and avidin-polymethacrylate sphere labels. For their gene mapping studies, Drs. Sodja and Davidson used DNA and RNA from *E.* coli and *Drosophila melanogaster*. Examples of their results obtained with this method are shown by the electron micrographs in Figures 2 and 4 which are published in the cited 1978 paper (Exhibit 2 of Dr. Sodja's Declaration) on pages 393 and 396, respectively. Furthermore, the authors found that gene enrichment was also efficiently obtained by buoyant banding of DNA:RNA-biotin:avidin-spheres in cesium chloride (CsCl) gradient. Results of the authors' enrichment experiments for 5S rRNA from Drosophila DNA are presented in Table II on page 398 in Dr. Sodja's 1978 paper (Exhibit 2 of her Declaration).

In Paragraph 12 (page 9), Dr. Sodja points out that at the time when she was conducting experiments related to her 1978 paper, she was neither thinking nor intending to attach a detectable non-radioactive label to the terminus of RNA for the purpose of making a nucleic acid hybridization probe. Rather, after hybridizing the modified RNA with DNA, Dr. Sodja was using large marker molecules, such as avidin-ferritin and avidin spheres, to produce more efficient gene mapping by electron microscopy and gene enrichment by cesium chloride gradient. In her work, Dr. Sodja oxidized the free 2', 3' OH groups of RNA to the dialdehyde form using periodate as described in her 1978 paper both in the reaction scheme outlined on page 386 (no. 1) and in the MATERIALS AND METHODS Section on page 387 under Preparation and Purification of RNA-Cytochrome-c:

> tRNA or 5S RNA were heated at 80° for 1-8 min in 1 mM NaAc buffer at pH 6.8, cooled, adjusted to 0.1 M NaAc buffer (pH 4.8) and treated with periodate as previously described (1). The amount of RNA used was 0.5 - 1 mg in 0.5 - 1 ml of reaction mixture.

Dr. Sodja notes that the publication cited as (1) above is Broker et al., "Electron microscopic visualization of tRNA genes with ferritin-avidin:biotin labels," also in Nucleic Acids Research, 5(2):363-384 (1978). A copy of Broker et al. is attached to Dr. Sodja's Declaration as Exhibit 7.

As a person of ordinary skill in the art, Dr. Sodja points out in Paragraph 13 (pages 9-10) that the periodate oxidation method used in her 1978 paper (Exhibit 2 of her Declaration) and in Broker et al. (Exhibit 7 of her Declaration) is applicable

only to RNA which has two vicinal OH groups at the 3' and 2' positions. Other nucleic acids, including DNA, do not possess an OH group on the 2' position. Thus, according to Dr. Sodja, the periodate oxidation method used in her 1978 paper (Exhibit 2) or Broker et al. (Exhibit 7) could not be used to attach a detectable non-radioactive label to DNA as set forth, for example, in claims 454 and 482 (see amendments to independent claims (Exhibit 4) and composite set of claims (Exhibit 5) in this application.

As a person of ordinary skill in the art, Dr. Sodja states in Paragraph 14 (page 10) that it is her opinion and conclusion that the claims 511 and 539 in this application, which claims are drawn to an oligo- or polynucleotide, are outside of her 1978 paper (Exhibit 2) or Broker et al. (Exhibit 7). Dr. Sodja states that as set forth in Paragraph 7C and 7D above, the amendments to the independent claims (Exhibit 4) and the composite set of claims, claims 511 and 539 contain the proviso that

> . . . provided that when said oligo- or polynucleotide is an oligoribonucleotide or a polyribonucleotide, and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

Clearly, according to Dr. Sodja, the fact that claims 511 and 539 eschew any and all chemical linkages which are obtained through a 2',3' vicinal oxidation of a terminal ribonucleotide, is significant because her 1978 paper relied exclusively on the vicinal oxidation of RNA using periodate. It is Dr. Sodja's opinion and conclusion that the subject matter of claims 511 and 539 would not have been taught or suggested to one of ordinary skill in the art at the time this application was first filed in June 1982 from reading her 1978 paper (Exhibit 2), taken with Gohlke's '458 Patent (Exhibit 6) and any of Applicants' admissions of record. As previously stated, the chemistry disclosed in Dr. Sodja's 1978 paper relied exclusively on vicinal oxidation of the free 2, 3' OH groups of RNA. The subject matter set forth in claims 511 and 539 clearly avoids such chemistry.

In Paragraph 15 (page 10), Dr. Sodja explains that at the time that she conducted the experiments disclosed in her 1978 paper, she was concerned that the chemistry would not work with oligoribonucleotides (10 ribonucleotides or less)

or very short polyribonucleotides. With such short pieces of RNA, she felt at the time that the addition of a large linker, such as cytochrome c, and a large biotin marker, might be too large in comparison to the length of the RNA such that steric hindrance would reduce, if not stymie hybridization between complementary RNA and DNA strands altogether.

Finally, in Paragraph 16 (page 11), Dr. Sodja states her understanding that in the obviousness rejections made in both the February 3, 1999 and July 18, 2000 Office Actions, the Gohlke '458 Patent was cited as the primary reference, and that her 1978 paper was cited as the secondary reference. This was explained on page 5 in the February 3, 1999 Office Action:

> it is Gohlke in view of Sodja which is the basis of the rejection. There is no evidence that Gohlke cannot be applied to Sodja for the expected benefit of generating other types of labeled oligonucleotides using the Gohlke labels.

It is Dr. Sodja's opinion and conclusion that even applying Gohlke's disclosed labels to her 1978 paper, one of ordinary skill in the art would not have arrived at the claimed invention in this application, as set forth in claims 454-567. As stated earlier, the chemistry used in Dr. Sodja's 1978 paper could not be applied to nucleic acids, such as DNA that lacked the 2' OH group otherwise found in RNA. Moreover, the claims drawn to the use of a terminal ribonucleotide as a modified nucleotide specifically avoid the vicinal oxidation and periodate chemistry described in Dr. Sodja's 1978 paper. Thus, according to Dr. Sodja, using Gohlke's labels with the chemistry from her 1978 paper, one of ordinary skill in the art would not have arrived at the invention now claimed in this application. Nor, according to Dr. Sodja, would such a person have had a reasonable expectation of success in reaching the present invention from a combined reading of Gohlke's 458 Patent, her 1978 paper and any statements made by the Applicants which are of record in this application.

In view of the submission of Dr. Sodja's Declaration (Exhibit B), Applicants respectfully request reconsideration and withdrawal of the first obviousness rejection.

The Second Rejection Under 35 U.S.C. §103

Claims 454-575 stand rejected under 35 U.S.C. §103 for being unpatentable over Halloran et al., J. Immunol. 96(3):373-378, 1966 or Miller et al. 20(7):1874-1880, 1981 for reasons of record. In the Office Action (pages 4-5), the Examiner stated:

> Both Halloran and Miller teach specific labels, (SIG moieties such as proteins and thiophosphates) attached to nucleic acids. See Halloran p. 373, Fig. 1 and col. 2; Miller p. 1874, col. 1. These prior art references differ from the claims in the recitation of some specific labels and linkages. It would have been prima facie obvious, however, to one of ordinary skill in the art at the time the invention was made to substitute any linker or label in the methods of Halloran and Miller for the expected benefit of constructing multiple labels. Given the fact that diverse labels such as proteins and thiophosphates, the ordinary artisan would have reasonably expected any moiety used as a label to function in the claimed invention.
>
> Repeating an important point from a previous Office action, applicants arguments to the 35 U.S.C. §112, first paragraph rejections have provided strong evidence of obviousness and vice-versa. For example, the references used to support enablement, Halloran and Miller add evidence of obviousness.
>
> It is important that the arguments for patentability explain, that the prior art supplied by applicant, for example Halloran and Miller, can buttress the specification--providing needed evidence that the thin "SIG Phosphate" disclosure both "describes" and "enables" the detailed invention now claimed--but that these same prior art references do not render the claims obvious.
>
> Furthermore, the criticisms of the obviousness rejections must be made without undermining the enablement rejection. For example, if arguing that Halloran and Miller are somehow "non-enabled" one must justify how the specification can be enabled. After all, the prior art contains much more detail than that found in the specification.
>
> Finally, the specification is held to a higher standard than the teachings of the prior art supplied in an obviousness rejection. As stated in a previous office action:
>
> > 35 U.S.C. § 112 provides that, in return for the grant of monopoly, the specification must enable one skilled in the art to "make and use" the invention without "undue experimentation" whereas 35 U.S.C. § 103 makes no such requirement. Thus, a teaching of how to use a compound can be entirely adequate to render a claim obvious but, at the same time, entirely inadequate to support the allowance of such a claim.

In response, Applicants again offer the Declaration of Dr. Cheryl H. Agris, Attorney At Law (Exhibit A)

In Paragraph 34 (page 29) of her Declaration (Exhibit A), Dr. Agris states that as a person of at least ordinary skill in the art to which the present invention pertains, it is her opinion and conclusion that the claimed subject matter at hand in the form of claims 454-567 would not have been obvious at the time the invention was made from a reading of either Halloran et al. or Miller et al. Dr. Agris's reasons for the non-obviousness of the invention of claims 454-567 are set forth in Paragraphs 35-39 (pages 29-31) as described below.

Dr. Agris notes in Paragraph 35 (page 29) that it was asserted in the last Office Actions that both Halloran et al. and Miller et al. teach specific labels and that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute any linker or label in the methods of Halloran and Miller for the expected benefit of constructing multiple labels. Dr. Agris also notes that in paragraph 11 of the February 3, 1999 Office Action, it was requested that arguments for patentability explain that the prior art supplied by applicant can buttress the specification providing needed evidence that the "SIG-phosphate" disclosure both "describes" and "enables" the detailed invention now claimed, but that these same prior art references do not render the claims obvious.

In Paragraph 36 (29-30), Dr. Agris responds to those statements in the Office Action. As one skilled in the art, it is Dr. Agris's opinion and conclusion that neither Halloran et al. nor Miller et al. actually disclose or suggest a "Sig-phosphate" moiety as defined in the Serial No. 08/479,997 specification. According to Dr. Agris, Halloran et al. is directed to covalently conjugating polynucleotides to proteins as a means of stimulating antibody formation and Miller et al. is directed to non-ionic oligonucleotide analogs. As explained by Dr. Agris, such analogs may be more easily taken up by cells than oligodeoxyribonucleotides and are resistant to cleavage by a variety of nucleases. According to Dr. Agris, neither of these modified polynucleotides were ever made for labeling purposes, nor were such use of Halloran's or Miller's modified polynucleotides ever suggested by the cited documents. Dr. Agris explains that neither the protein in Halloran et al. nor the methyl group in Miller et al. would be considered a detectable label as defined in the art or a detectable Sig chemical moiety as defined in the '997 specification. Before the advent of the invention now claimed, explains Dr. Agris,

there had been no suggestion regarding attaching a Sig group, that is, a moiety capable of non-radioactive detection when attached to the phosphate moiety of at least one nucleotide in an oligo- or polydeoxyribonucleotide or polynucleotide.

As one skilled in the art to which this invention pertains, Dr. Agris points out in Paragraph 37 (page 30) that there had been teachings regarding modifying the phosphate moiety with various substituents, but none of these substituents comprised a Sig-phosphate as set forth in the present claims. Once such a concept for modifying the phosphate moiety of a nucleotide was formulated, according to Dr. Agris, one of ordinary skill in the art would have looked to prior art references in order to develop methods for obtaining the oligo- or poly(deoxyribo)nucleotides of the present invention. As a specific example, Dr. Agris notes that Halloran et al. disclosed methods for coupling proteins to nucleotides and oligonucleotides. This reference may be used, according to Dr. Agris, as a general reference for coupling amino acid moieties to the phosphate moiety. As explained by Dr. Agris, there is no disclosure in Halloran et al., however, that a final oligo- or poly(deoxyribo)nucleotide comprising at least one modified nucleotide of the formula set forth in the pending claims could be obtained.

In Paragraph 38 (pages 30-31) of her Declaration, Dr. Agris states that with respect to the cited Miller reference, she is very familiar with the chemistry employed to make oligonucleoside methylphosphonates, having been a graduate student in Dr. Paul Miller's laboratory during the years 1979-1986. During that time according to Dr. Agris, she and other members of Dr. Miller's group looked to procedures published on obtaining oligonucleotides in order to synthesize oligonucleoside methylphosphonates. For example, the condensing agent used in the cited Miller et al. reference, mesitylene sulfonyl tetrazolide, was used in synthesizing oligonucleotides. A copy of Stawinski et al. [Nucleic Acids Research 4:353-371 (1977)] which describe the use of mesitylene sulfonyl tetrazolide in synthesizing oligonucleotides is attached as to Dr. Agris's Declaration as Exhibit 9. Also attached to Dr. Agris's Declaration is section II.A. of my Ph.D. thesis (Exhibit 2) detailing strategies used in synthesizing oligonucleoside methylphosphonates. Although her thesis was not submitted until January 1986, Dr. Agris notes that the synthetic work described on pages 13-16 actually took place between 1979-1983. Dr. Agris was personally involved in synthesizing oligonucleoside

methylphosphonates in June 1982. As described in those pages from Dr. Agris's thesis, methods known in the art for synthesizing oligodeoxyribonucleotides were used as a basis for synthesizing oligonucleoside methylphosphonates. However, according to Dr. Agris, neither she nor in my opinion, others of ordinary skill in the art had a reasonable expectation of success that these procedures could be successfully used in preparing oligonucleoside methyl phosphonates. For example, Stawinski et al. (Exhibit 9) merely provided a starting point regarding possible reaction conditions that could be used. There is no suggestion in Stawinski et al., however, that arylsulfonyltetrazoles could or even should be used to synthesize oligonucleoside methylphosphonates. Dr. Agris avers that the references cited were primarily used as guidelines for trying to formulate methods for synthesizing oligonucleoside methylphosphonates.

In the final paragraph of her Declaration (39), Dr. Agris states that it appears that the Miller and Halloran references were used as guidelines in formulating the oligo- or poly(deoxyribo)nucleotides of the present invention. The disclosures in each of these references would be sufficiently enabling for one of ordinary skill in the art for formulating procedures for synthesizing the oligo- or poly(deoxy)ribonucleotides of the present invention. According to Dr. Agris, there was no suggestion, however, that these procedures could or should be used to obtain, nor would one of ordinary skill in the art have a reasonable expectation of success in obtaining the oligo- or poly(deoxy)ribonucleotides of the present invention. Thus, it is Dr. Agris's opinion and conclusion that a person of ordinary skill in the art would not have arrived at the invention claimed in U.S. Patent Serial No. 08/479,995 from a reading of the cited Miller or Halloran references, or even by combining the two references.

In light of Dr. Agris's Declaration (Exhibit A) and her statements on the non-obviousness of the present invention, Applicants respectfully request that the second obviousness rejection be withdrawn upon further reconsideration.

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SUMMARY AND CONCLUSIONS

Claims 454-566 are presented for further examination. Claims 454-455, 459, 461, 466, 476, 482-483, 487, 489, 494, 504, 508, 510-531, 533, 535-559, 561 and 563-567 have been amended. Claims 568-575 have been canceled hereinabove. Thus, 454-567 as amended are presented for further examination in this application.

This Amendment is accompanied by a Request For An Extension Of Time (3 Months) and authorization for the fee therefor. Also accompanying this Amendment is a Notice of Appeal and authorization for the fee therefor. No other fee or fees are believed due in connection with this filing. In the event that any other fee or fees are due, however, authorization is hereby given to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

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